

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Modeling lifetime costs and health outcomes attributable to secondhand smoke exposure at home among Korean adult women
AUTHORS	Lee, Jiya; Han, Ah Ram; Choi, Dalwoong; Lim, Kyung-Min; Bae, SeungJin

VERSION 1 - REVIEW

REVIEWER	Nirupama Putcha Johns Hopkins University School of Medicine Baltimore, MD USA
REVIEW RETURNED	25-Sep-2016

GENERAL COMMENTS	<p>Lee and colleagues analyze Korean epidemiological data to understand the contribution of secondhand smoke exposure to quality of life, health care expenditures and mortality in Korean women. The analysis appears to be well conducted and the results are interesting, but would benefit from a few clarifications.</p> <p>1. It would be helpful to better describe the population of women over the age of 40 in Korea, particularly early in the manuscript (intro, methods perhaps). Perhaps I am mistaken but it seems that a fundamental assumption is that women in this age group do not spend a lot of time outside of the home (since this is the only source of SHS that is discussed). Is this an appropriate assumption? If not this should be addressed up front and also discussed in limitations as to why this changes the generalizability of the study findings.</p> <p>2. Did the authors consider the value of accounting for primary smoking in the population studied? What is the proportion of primary smoking in this age group of Korean women and would it be helpful to consider this in the study measures? SHS can still have an impact on those with primary smoking exposure so it would be interesting to consider this.</p> <p>3. The health conditions considered in the health outcome measurements did not include COPD, and the authors state this is because of a lack of consensus about the link between SHS exposure and COPD. However, what about chronic bronchitis?</p> <p>4. In general there were some very interesting findings of the study, and it would be valuable to include more interpretation in the discussion section to help the reader put this work into context. Instead, currently the discussion section goes only slightly beyond restating the results. It would be helpful to include more interpretation, referring back to the literature. For example, why do the authors think that SHS exposure had more impact on quality of life instead of life expectancy? This is a very interesting finding and it</p>
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	would be helpful to delve more into this with more interpretation of these findings.
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REVIEWER	Gary Ginsberg Ministry of Health Jerusalem Israel
REVIEW RETURNED	01-Jan-2017

GENERAL COMMENTS	<p>Very clear paper --- just a few minor revisions needed</p> <p>1) Page 6:(please add in the conditions in brackets -- I am aware you mentioned them in the discussion) "Health conditions (COPD, Breast Cancer, cervical cancer) that were reported</p> <p>2) page 9 line 26 160, 130 should be written as 160,130</p> <p>3) page 9 line 28 authros should be authors</p> <p>4) page 8 35-39....rewrite sentence as "we refereed to Jee and colleagues study because.....</p> <p>5) page 9 line 8....please add in ONE sentence briefly explaining what the "MACRO COSTING APPROACH IS"</p> <p>6) page 9 line 15.....state exchange rate used to convert Korean Currency to USD.</p> <p>7) Page 12 line 42....adjust the finding of \$44.58 to p[resent day values as paper was published in 2009.</p> <p>8) page 12 line 47..... I beleive the studies reported LOWER incremental costs not HIGHER incremental costs --- please check</p> <p>9) Finally please add 95% Confidence Intervals ntervals to all the stated results.....</p>
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REVIEWER	TSIKRIKA STAMATOULA Pulmonary Division, Department of Critical Care, University of Athens Medical School, Evangelismos Hospital, Athens, Greece
REVIEW RETURNED	03-Jan-2017

GENERAL COMMENTS	<p>Please, comment on:</p> <ul style="list-style-type: none"> - limited time of the study - self reported exposure in their homes - exposed to SHS rather than their home settings (neighbouring) - current reported SHS exposure and not occured in the past
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REVIEWER	Woohyeon Kim Korea Institute of Public Finance, Republic of Korea (South Korea)
REVIEW RETURNED	13-Jan-2017

GENERAL COMMENTS	<p>Lee and colleagues estimated lifetime costs and health outcomes for 40-year old Korean women who were at risk of second-hand smoking (SHS) exposure via Markov simulation model. They found that the negative impact of SHS exposure was greater on Quality-Adjusted Life Years than on life expectancy. In addition, it was estimated that the Korean adult women exposed to SHS paid an additional \$600 medical costs compared with female not exposed. My biggest concern is the authors assume that the model is progressive in nature; i.e. once a patient suffers from one of four</p>
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	<p>diseases, she cannot move into the event-free state. According to the model, a lung cancer patient should pay \$6,584 per year with the constant utility of 0.50 in her remaining lifetime even after she fully recovers from the disease. The assumption may simplify the model, but does not sound realistic to me. The authors may want to provide any scientific evidence why the model should be progressive. For example, a lung cancer patient might not fully recover from the disease, so they may end up receiving a permanent post-surgery treatment. (I do not have any professional medical knowledge on this. This is just an example.)</p> <p>Only 4 main diseases were considered in their Markov model. The authors also mentioned that this may lead to a conservative conclusion since SHS exposure may be associated with other diseases. It would be helpful for readers to understand how rigorous the authors measured lifetime SHS exposure costs if they could provide any evidence how these 4 diseases are closely related to smoking and/or SHS. In addition, I cannot guess whether these 4 main health conditions contribute to a significant portion of the overall lifetime SHS-related medical costs. They may relate to only a part of lifetime SHS-related medical costs, which limit the scope of this study.</p> <p>The authors claim that (1) “the adverse impact of SHS exposure on health outcomes was more likely to occur during the later part of the time horizon” and (2) “the direct healthcare costs associated with SHS exposure were likely to occur during the earlier part of the time horizon”. These two findings may be contradictory to each other as far as I understand. The authors may want to elaborate on the meaning of these findings and deliver a clear idea why the incidence of the adverse impact of SHS exposure does not coincide with the incurrence of the medical costs.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Q1. It would be helpful to better describe the population of women over the age of 40 in Korea, particularly early in the manuscript (intro, methods perhaps). Perhaps I am mistaken but it seems that a fundamental assumption is that women in this age group do not spend a lot of time outside of the home (since this is the only source of SHS that is discussed). Is this an appropriate assumption? If not this should be addressed up front and also discussed in limitations as to why this changes the generalizability of the study findings.

A1. We thank the Reviewer for the thoughtful comment.

It has been reported that the dominant places for secondhand smoke (SHS) exposure were home and workplaces (US Department of Health and Human Services, 2006), where the former was significantly higher than the latter, based on survey and urinary cotinine level measurement (Eisner, Katz, Yelin, Hammond, & Blanc, 2001; Riboli et al., 1990).

The importance of SHS exposure at home can be explained by the World Health Organization's Framework Convention on Tobacco Control (WHO FCTC), which bans public indoor smoking and has been legally binding in Korea since 2003. Thus, it is highly probable that most of SHS has occurred inside their residence.

This notion is further supported by two studies on Asian women suggesting that husband's smoking was the only factor significantly associated with wives' morbidity from lung cancer (Hirayama, 1984;

Jee, Ohrr, & Kim, 1999),

We described these points in the introduction as follows:

“SHS in workplace is becoming less of an issue in many developed countries thanks to smoke-free laws that have banned smoking in public places, large buildings and restaurants(Max, Sung, & Shi, 2015; Plescia, Wansink, Waters, & Herndon, 2011). However, few policies have been aggressive enough to ban smoking at home, leaving non-smokers in households exposed to SHS. Yet, measured nicotine and cotinine concentrations were significantly higher at home than at work, suggesting that SHS at home are predominant health concerns(Eisner et al., 2001; Riboli et al., 1990).”

Q2. Did the authors consider the value of accounting for primary smoking in the population studied? What is the proportion of primary smoking in this age group of Korean women and would it be helpful to consider this in the study measures? SHS can still have an impact on those with primary smoking exposure so it would be interesting to consider this.

A2. As we described in the original manuscript, the rate of primary smoking among Korean women is substantially lower than men (4.3% versus 36.2%) as of 2013, whereas the Organization for Economic Cooperation and Development (OECD) reported that the average percentage of men and women smokers are 24.2% and 15.5%, respectively(OECD Indicators). Moreover, the age group of Korean women we studied showed even lower rate of primary smoking (5%, 2.5%, and 3.8% for women in their 40s, 50s and 60 & older, respectively). Thus, the impact of primary smoking in this age group would be minimal(Korean Ministry of Health and Welfare, 2015).

Q3. The health conditions considered in the health outcome measurements did not include COPD, and the authors stated this is because of a lack of consensus about the link between SHS exposure and COPD. However, what about chronic bronchitis?

A3. As Reviewer 1 has suggested, chronic bronchitis was reported to be associated with passive smoking, yet it has been reported that the link was limited to children exposed to parental smoking (Öberg et al., 2010; US Department of Health and Human Services, 2006), which is not the population of interest in our study.

We hope that our reply will clear the reviewer’s concern

Q4. In general there were some very interesting findings of the study, and it would be valuable to include more interpretation in the discussion section to help the reader put this work into context. Instead, currently the discussion section goes only slightly beyond restating the results. It would be helpful to include more interpretation, referring back to the literature. For example, why do the authors think that SHS exposure had more impact on quality of life instead of life expectancy? This is a very interesting finding and it would be helpful to delve more into this with more interpretation of these findings.

A4. Thanks for favorable opinion on our study.
We added following sentences in our manuscript.

“Since the diseases caused by SHS exposure are likely to be of chronic nature but not of high mortality (such as asthma or MI), the exposed women are likely to suffer from diseases caused by SHS exposure, thus their quality of life decreased, while their life expectancy is similar to that of the non-exposed. Thus, it is not surprising that we reached such conclusions”.

Also, lines of epidemiological evidence support that SHS exposure increases the disease incidence rate rather than the mortality rate (Jaakkola, Piipari, Jaakkola, & Jaakkola, 2003; US Department of Health and Human Services, 2006).

Reviewer 2

Q1. Page 6: (please add in the conditions in brackets -- I am aware you mentioned them in the discussion)

"Health conditions (COPD, Breast Cancer, cervical cancer) that were reported.

A1. The sentence has been changed as suggested by the reviewer.

Q2. page 9 line 26 160, 130 should be written as 160,130

A2. The sentence has been changed as suggested by the reviewer.

Q3. page 9 line 28 authros should be authors.

A3. The typo has been corrected as suggested.

Q4. page 8 35-39....rewrite sentence as "we refereed to Jee and colleagues study because.....

A4. The sentence has been edited as suggested.

Q5. page 9 line 8....please add in ONE sentence briefly explaining what the "MACRO COSTING APPROACH IS"

A5. We added the following sentence.

““macro-costing” techniques, wherein total cost per case is modeled as a function of a set of predictor variables (e.g., disease type, demographics, health system attributes), setting the stage for efficient derivation of cost-per-case estimates, conditional on these covariates.”

Q6. page 9 line 15.....state exchange rate used to convert Korean Currency to USD.

A6. 1 USD equals 1,053.22 Korean won as of 2014.

Q7. Page 12 line 42.adjust the finding of \$44.58 to present day values as paper was published in 2009.

A7. The value has been adjusted in 2014 USD and the sentence has been changed as follows:

“\$51.66 in 2014, adjusted by the medical care component of CPI

Q8. page 12 line 47..... I believe the studies reported LOWER incremental costs not HIGHER incremental costs --- please check

A8. In the page 12, we wrote "Waters and colleagues analyzed the direct healthcare costs related with SHS exposure among Minnesota residents, and concluded that SHS exposure is associated with \$44.58 (or \$51.66 in 2014) per resident per year(Waters, Foldes, Alesci, & Samet, 2009). Max and colleagues reported that SHS was responsible for \$241 million in healthcare cost and \$119 million in lost productivity costs, resulting in \$213 per non-smoker in California exposed to SHS(Max et al., 2015). Those studies reported a higher incremental cost compared with ours". Since the underlined figures in the previous studies were yearly base, it is correct that our costs, which are based on life-time, are lower. The reasons behind this was further explained as follows, "Those studies reported a higher incremental cost compared with ours, which could be attributed to our conservative assumptions, such as excluding children and the loss of the productivity costs, only including health conditions with relative risks that are significantly increased, and assuming no utility difference between the SHS exposure status. Also, the healthcare cost in Korea is generally lower than that in the US thanks to Korea's National Health Insurance system. Thus, our healthcare cost estimate could actually underestimate the effect of the SHS exposure. Our estimate could refer to the lower bound of the healthcare costs associated with SHS exposure." We hope that this could clarify the point.

Q9. Finally please add 95% Confidence Intervals to all the stated results.

A9. Unlike probabilistic sensitivity analyses which consider each patient individually and allow for variability by incorporating distributional uncertainty, our base case analyses are based on a Markov cohort simulation model, which estimates the average cost and health consequences of hypothetical cohort, thus results are only shown in point estimates(Siebert et al., 2012; Sonnenberg & Beck, 1993). Previous studies using Markov cohort simulation models also presented point estimates only(Godfrey, Ali, Parrott, Pickett, & Consortium, 2011; Knight, Boler, & Baker, 2008). To evaluate the robustness of the analyses, we conducted several sensitivity analyses with different assumptions (Table 3), and probabilistic sensitivity analysis was conducted and the distribution was visually presented in Supplementary Figure 1. We have added the 95% interval in the Supplementary Figure 1.

Reviewer 3

Q1. Limited time of the study

A1. We understand this as commenting on limiting starting age of the target population to 40 years. The increased risks caused by SHS exposure in our study were obtained from previous studies, and most of those studies on spousal SHS exposure have defined age group as 40 and older(Jee et al., 1999; Oono, Mackay, & Pell, 2011; Thun, Henley, & Apicella, 1999; Wen et al., 2006).

Q2. Self- reported exposure in their homes

A2. Based on Korean national survey in 2014, about 13.9% of female non-smoking adults are exposed to SHS at home(Korean Ministry of Health and Welfare, 2015). It has been reported that about 13.9 million Korean females are aged 40 or older as of January 2016, thus about 1.9 million adult Korean females are estimated to be exposed to the SHS exposure at home, which translates into 1.16 Billion USD (13.9 million *incremental medical cost due to SHS exposure (600 incremental

USD per person exposed to SHS) at national level.

Q3. exposed to SHS rather than their home settings

A3. We thank the reviewer for the thoughtful comment.

It has been reported that the dominant places for secondhand smoke (SHS) exposure were home and workplaces (US Department of Health and Human Services, 2006), where the former was significantly higher than the latter, based on survey and urinary cotinine level measurement (Eisner et al., 2001; Riboli et al., 1990).

The importance of SHS exposure at home can be explained by the World Health Organization's Framework Convention on Tobacco Control (WHO FCTC), which bans public indoor smoking and has been legally binding in Korea since 2003. Thus, it is highly probable that most of SHS has occurred inside their residence.

This notion is further supported by two studies on Asian women suggesting that husband's smoking was the only factor significantly associated with wives' morbidity from lung cancer (Hirayama, 1984; Jee et al., 1999),

We described these points in the introduction as follows:

"SHS in workplace is becoming less of an issue in many developed countries thanks to smoke-free laws that have banned smoking in public places, large buildings and restaurants (Max et al., 2015; Plescia et al., 2011). However, few policies have been strenuous enough to ban smoking at home, leaving non-smokers in households unprotected from SHS. Further supporting this, environmental nicotine exposure were significantly and incomparably higher at home than at work, suggesting that SHS at home are predominant health concerns (Eisner et al., 2001; Riboli et al., 1990)."

We hope that our reply and revision have cleared the reviewer's concern.

Q4. current reported SHS exposure and not occurred in the past.

A4. As the reviewer pointed out, the SHS-attributable risks in our study were generalizable to non-smoking female adults (40 years or older) exposed to current smokers, and we did not consider the SHS exposure in the past.

Since most of the epidemiological studies we referred to considered spousal current smoking status from this age and ignored whether those women had been exposed to the SHS in the past, we followed this norm (Jee et al., 1999; Lee & Forey, 2006; Oono et al., 2011). Therefore, we acknowledge that this is a limitation which needs to be addressed. Following sentence has been added in the discussion as a limitation.

"Our study was based on the current reported SHS exposure but did not consider SHS occurred in the past based on the previous epidemiological studies, which should be interpreted with caution."

Reviewer 4

Q1. Lee and colleagues estimated lifetime costs and health outcomes for 40-year old Korean women who were at risk of second-hand smoking (SHS) exposure via Markov simulation model. They found

that the negative impact of SHS exposure was greater on Quality-Adjusted Life Years than on life expectancy. In addition, it was estimated that the Korean adult women exposed to SHS paid an additional \$600 medical costs compared with female not exposed.

My biggest concern is the authors assume that the model is progressive in nature; i.e. once a patient suffers from one of four diseases, she cannot move into the event-free state. According to the model, a lung cancer patient should pay \$6,584 per year with the constant utility of 0.50 in her remaining lifetime even after she fully recovers from the disease. The assumption may simplify the model, but does not sound realistic to me. The authors may want to provide any scientific evidence why the model should be progressive. For example, a lung cancer patient might not fully recover from the disease, so they may end up receiving a permanent post-surgery treatment. (I do not have any professional medical knowledge on this. This is just an example.)

A1. Thanks for the kind comments.

We employed a Markov cohort simulation model, which is particularly suited to modelling chronic diseases (Siebert et al., 2012; Sonnenberg & Beck, 1993), where patients experience disease progression over time, and has been frequently employed in active smoking simulation models (Godfrey et al., 2011; Linden et al., 2010). In Markov cohort model, each state is assumed to be homogeneous; namely, every individual in that state has the same transition probabilities, implying that any characteristics that determine those probabilities must not differ within the state (Siebert et al., 2012). Thus if we assume the patients can fully recover and move back to event-free states, then the probability of having lung cancer for those who recovered from lung cancer would be same as those who never had lung cancer, which is contradictory to currently available evidences, namely, patients who recovered from lung cancer are recommended to receive more frequent examinations to check the recurrence of lung cancer, like H&P and low-dose non-contrast enhanced chest CT annually, since their recurrence rates are higher (National Comprehensive Cancer Network, 2016), which explains why the cost of lung cancer last for lifetime.

Q2. Only 4 main diseases were considered in their Markov model. The authors also mentioned that this may lead to a conservative conclusion since SHS exposure may be associated with other diseases. It would be helpful for readers to understand how rigorous the authors measured lifetime SHS exposure costs if they could provide any evidence how these 4 diseases are closely related to smoking and/or SHS.

A2. We sought to estimate cost and health outcomes attributable to SHS exposure among adults by incorporating the health outcomes based on previous systematic reviews and recommendations.

Reports from US Surgeon General (US Department of Health and Human Services, 2006), WHO (Öberg et al., 2010) were referred and we identified health conditions proved to be caused by SHS exposure among adults; US Surgeon general concluded that lung cancer and coronary heart diseases were caused by the SHS, whereas the WHO concluded that adult onset asthma, ischemic heart disease and lung cancer were caused by SHS.

We also referred to studies evaluating the economic cost of SHS, which estimated SHS-attributable costs by identifying diseases caused by the SHS exposure; namely, lung cancer, ischemic heart disease, and asthma (McGhee et al., 2006; Plescia et al., 2011)

To incorporate studies published subsequent to the publication of reports from US Surgeon General and WHO, we also searched Pubmed, Embase, Cochrane Database of Systematic Review whose populations were adult female, exposed to SHS/passive smoking/involuntary smoking/ environmental tobacco smoke, whose study designs were systematic reviews or meta-analysis to identify which health conditions were caused by the SHS exposure. As a result, stroke was included since recently published meta-analysis confirmed causal relationship between stroke and SHS exposure (Oono et

al., 2011).

And this approach is in line with the previous reports: Plescia and colleagues determined 2 conditions (lung cancer and coronary heart diseases) were caused by SHS exposure(Plescia et al., 2011), based on US Surgeon General's recommendations with highest level of evidence(US Department of Health and Human Services, 2006). An Asian study included four conditions (lung cancer, stroke, pulmonary diseases, ischemic heart diseases) for estimating medical costs of passive smoking(McGhee et al., 2006).

Following sentences have been added in the manuscript

"We considered 4 major health outcomes based on previous systematic reviews and official recommendations(Jaakkola et al., 2003; Öberg et al., 2010; Oono et al., 2011; Taylor, Najafi, & Dobson, 2007; US Department of Health and Human Services, 2006) and conditions whose causal association was inconclusive (such as breast cancer, COPD, cervical cancer)were not included(Öberg et al., 2010; US Department of Health and Human Services, 2006)"

Q3. In addition, I cannot guess whether these 4 main health conditions contribute to a significant portion of the overall lifetime SHS-related medical costs. They may relate to only a part of lifetime SHS-related medical costs, which limit the scope of this study.

A3. As Reviewer 4 has pointed out, our SHS-associated costs were based on 4 health conditions, and conditions whose causal association was inconclusive (such as breast cancer, COPD, cervical cancer)were not included, thus we suggested that our estimate is conservative

In previous studies estimating medical cost of passive smoking among adults, Plescia and colleagues determined 2 conditions (lung cancer and coronary heart diseases) were caused by SHS exposure(Plescia et al., 2011), based on US Surgeon General's recommendations with highest level of evidence(US Department of Health and Human Services, 2006). An Asian study included four conditions (lung cancer, stroke, pulmonary diseases, ischemic heart diseases) for estimating medical costs of passive smoking, thus our estimation of medical costs caused by those 4 conditions were consistent with previous studies.

Q4. The authors claim that (1) "the adverse impact of SHS exposure on health outcomes was more likely to occur during the later part of the time horizon" and (2) "the direct healthcare costs associated with SHS exposure were likely to occur during the earlier part of the time horizon". These two finding may be contradictory to each other as far as I understand. The authors may want to elaborate on the meaning of these findings and deliver a clear idea why the incidence of the adverse impact of SHS exposure does not coincide with the incurrence of the medical costs.

A4. Thanks for a crucial comment. As the reviewer pointed out, the description should be elaborated. The economic impact of the SHS exposure had higher impact in the later part of the time horizon, along with health outcomes. This claim was confirmed in the Figure 2A, where the expected costs of two groups increased as the age of the population increased. We have added following sentences, and those misleading descriptions have been revised as well.

Those sentences have been changed as follows in the DISCUSSION:

"the model illustrated that SHS exposure-attributable health costs and negative health outcomes have higher impact on older adults (e.g. their 70s) than younger ones (e.g.in their 50s), which is attributable to the longer exposure of SHS, implying that the impact of SHS exposure is cumulative and progressive; thus, aggressive smoking bans or education on SHS at home as early as possible might be needed for those women who married current smokers, even though individuals in those age

groups may not suffer from premature deaths.

Following sentences have been changed in the RESULTS:

“The negative economic impact of SHS exposure escalated as the time horizon increased (from 64 USD for 5 years to 472 USD for 20 years), since the projected value for 20 years is more than 4 times of the values projected for 5 years, suggesting that the direct healthcare costs associated with SHS exposure have higher impact on the later part of the time horizon.”

The ABSTRACT has been changed as follows:

“The negative impact of SHS exposure on health outcomes and healthcare costs escalated as the time horizon increased, suggesting that the adverse impact of SHS exposure on health outcomes and healthcare costs may have higher impact on the later part of the lifetime”

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VERSION 2 – REVIEW

REVIEWER	Gary Ginsberg Ministry of Health, Israel
REVIEW RETURNED	15-Feb-2017

GENERAL COMMENTS	The authors have responded to my comments in a satisfactory manner
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REVIEWER	TSIKRIKA STAMATOULA Pulmonary Division, Department of Critical Care, University of Athens Medical School, Evangelismos Hospital, Athens, Greece, Evangelismos Hospital, Athens
REVIEW RETURNED	05-Mar-2017

GENERAL COMMENTS	<p>This article estimates the healthcare costs and health related quality of life of SHS exposure among non-smoking Korean women compared with those not exposed at home. As shown, the negative impact of SHS increase healthcare costs and decreases their life expectancy in non-smoker spouses with domestic exposure. This topic seems to be very interesting in conducting strict domestic smoke free laws and also in health care costs which are not well understood in less developed countries.</p> <p>The introduction is clear and concise and gives a good rationale for why studying SHS exposure and its effect on Korean non-smoking women aged 40 and married to current smokers. All the figures and tables are easily readable, correct and informative. This paper presents novelty and originality of research, importance and impact of results on their health hazard and financial aspect of health</p>
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	<p>consequences due to SHS.</p> <p>Overall, this is a study on the effects of domestic exposure to smoke in a specific population, and in terms of healthcare costs and health-related quality of life. The authors have adequately addressed the reviewers' comments and concerns.</p>
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